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Original Article

Vascular mortality rates and effects of hematological inflammatory markers on in-hospital mortality in patients with acute ischemic stroke

Muzaffer Gunes

Department of Neurology, Faculty of Medicine, Aksaray University, Aksaray, Turkey

Abstract

Aim: Inflammatory markers that may be associated with on the prognosis of acute ischemic stroke (IS) such as C-reactive protein/albumin ratio, neutrophil/lymphocyte ratio, albumin, red blood cell distribution width (RDW) have been investigated in the recent years. In this study, it was aimed to investigate the effects of all these inflammatory markers on in-hospital mortality and to determine the mortality rates due to cerebral artery occlusion in patients with acute IS.

Materials and Methods: Patients hospitalized in our hospital with a diagnosis of acute IS between April 2014 and August 2018 were retrospectively analyzed. Logistic regression analysis was used to investigate the prognostic factors in IS. Receiver operating characteristic (ROC) curve analysis was performed to calculate the cut-off values and evaluate the predictive values of variables.

Results: 344 patients, including 267 patients who were alive and 77 patients who died at the hospital, were included in the study. The infarcts that had the highest mortality rate were massive infarcts in the internal carotid artery area (75%), middle cerebral artery-M1 segment infarctions (62.5%) and total basilar artery infarcts (40%). According to the multivariate logistic regression model, only RDW-SD and albumin were found to be poor prognostic factors of IS (p=0.005 and p=0.021). Area under the ROC curve was as follows: RDW-SD 0.613 (95% CI, 0.53-0.69).

Conclusions: High RDW-SD and low albumin levels at admission are independent poor prognostic factors of acute IS. Multicenter studies conducted with large patient populations are necessary to determine vascular mortality rates in patients with IS.

Keywords: Albumin; C-reactive protein/albumin ratio; ischemic stroke; neutrophil/lymphocyte ratio; red blood cell distribution width; vascular mortality rates

INTRODUCTION

Stroke is one of the important causes of disability and death in the adult population (1). Age and severity of stroke are the most important factors that affect mortality (2). Recently, hematological inflammatory factors affecting the prognosis of acute ischemic stroke (IS) have been investigated (3). Red blood cell distribution width (RDW) was found to have a positive correlation with well-known inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate. Therefore, it is emphasized that it can be used as a marker reflecting inflammation (3,4). Studies have revealed an association between the hematological inflammatory markers, i.e. neutrophil-to-lymphocyte ratio (NLR) (5,6), neutrophil/eosinophil ratio (7) and RDW (3,8,9), and prognosis of stroke.

It was found in a study that a high C-reactive protein/albumin ratio (CAR) was an independent predictor of 90-day mortality in patients with acute IS (10). CRP and albumin are acute phase proteins that indicate systemic inflammation (11,12). Elevated CRP and decreased albumin levels can be observed in patients with inflammation (11-13). This may have a negative impact on the prognosis of patients. It was recently found that CAR, calculated by dividing CRP by albumin, is a novel potential marker of inflammation and plays a role in the prognosis of various diseases (10,14,15).

To the best of our knowledge, there are no studies that investigate the mortality rates of all occluded cerebral arteries together in patients with IS in the literature. In addition, studies that investigate NLR, albumin, CAR and RDW together are also lacking. That's why, this retrospective study aimed to determine the mortality rate associated with the occluded arteries and to investigate the effects of NLR, albumin, CAR and RDW on in-hospital mortality in patients with acute IS.

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Corresponding Author: Muzaffer Gunes, Department of Neurology, Faculty of Medicine, Aksaray University, Aksaray, Turkey
E-mail: drmuzaffergunes@gmail.com

MATERIALS and METHODS

This study was conducted with the patients who were hospitalized with the diagnosis of acute IS at Aksaray University Training and Research Hospital between April 2014 and August 2018. 752 patients with IS were retrospectively studied. Parenchymal and vascular images of the brain were initially examined in patients who died at the hospital and the occluded cerebral arteries were identified from the images (Table 1 lists the arteries contributed to the mortality). Patients who did not die although they had occlusion in the same arteries were included in the study as controls. The inclusion criteria were as follows: being older than 18, no history of intravenous thrombolytic therapy and/or mechanical thrombectomy and a symptom-to-door time shorter than 24 hours. The exclusion criteria were as follows: presence of cerebral artery occlusion that did not cause death, a symptom-to-door time longer than 24 hours, being younger than 18, presence of a hematologic disease and missing data. In total, 344 patients met the inclusion criteria.

When patients are admitted to our hospital with a pre-diagnosis of stroke, the first step is to obtain medical history from the patient or their relatives very quickly. The vital signs are also measured and blood glucose level is measured from the fingertip. Blood samples are taken for the biochemical analysis, while performing neurological examination. Diffusion-weighted magnetic resonance imaging (MRI) or computed tomography (CT) of the brain is performed to obtain parenchymal images of the brain. Moreover, MR angiography or CT angiography is performed to obtain vascular images of the brain. Then, the patients are provided with the suitable treatment.

In this study, laboratory data obtained during admission to the emergency department were used. Laboratory analyzes of the patients were performed in our institution's hematology laboratory. Venous blood samples were taken from all patients for a complete blood count and were performed using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan) in the hematology department (7, 9). NLR was calculated by dividing the neutrophil count by the lymphocyte count, and CAR, by dividing the amount of C-reactive protein by the amount of albumin.

Brain vascular and parenchymal imaging results, clinical data and laboratory findings of the patients were taken from our database and recorded for the statistical analysis. The study was approved by the ethics committee of Aksaray University, protocol number 2020 / 06-40, and was carried out in accordance with the Declaration of Helsinki.

Statistical analysis

The results of this study are expressed as mean ± standard deviation for normally-distributed data, median (minimum- maximum) for abnormally-distributed data and percentage (%). Kolmogorov-Smirnov normality test was used to examine the distribution pattern of the data. Because only red blood cell (RBC) data distributed normally, thus were compared using Student's independent samples T test. Since blood test parameters other than RBC did not show normal distribution, these parameters were compared with the Mann Whitney-U test. Univariate and multivariate logistic regression analysis tests were used to investigate factors associated with mortality in IS. First of all, variables with a P-value less than 0.25 for primary comparison were included in the univariate logistic regression model. Subsequently, variables with a P-value less than 0.1 in univariate logistic regression analysis were included in the multivariate logistic regression model. Hosmer-Lemeshow test was used for goodness of fit of the model. Consistency between variables was evaluated by Cox & Snell pseudo-R^2 and Nagelkerke pseudo-R^2 tests. The receiver operating characteristics (ROC) curve analysis test was used to evaluate the predictive value of the variables and to calculate the cut-off values. If the area under the ROC curve is 0.5, the model does not discriminate; 0.5-0.7, the model has poor to fair discrimination; 0.7-0.8, the model has acceptable discrimination; 0.8-0.9, the model is perfect; 0.9-1.0, is accepted as a very rare outcome (16). For statistical analysis of all data, SPSS 23.0 was used software for Windows (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

RESULTS

A total of 344 patients with acute IS were eligible for the study. The patients without hospital mortality group (survivors) consisted of 267 patients [122 males and 145 females, median age: 72 (24-98)] and the patients with in-hospital mortality (non-survivors) group consisted of 77 patients [28 males and 49 females, median age: 79 (47-99)]. Overall mortality rate in IS was 22.4%. Table 1 presents the mortality rates of IS according to affected blood vessels. The vessels that caused the highest number of deaths and the mortality rates were as follows: Massive infarcts in the internal carotid artery (ICA) area (75%), middle cerebral artery (MCA)-M1 segment infarctions (62.5%) and total basilar artery infarcts (40%).

Blood parameters between groups (survivors and non-survivors) are compared in Table 2. According to the Student's T test, the mean RBC was significantly lower in the patients non-survivors compared to the patients survivors ($p = 0.046$). Mann Whitney U test revealed that the median white blood cell (WBC), hemoglobin, monocyte, hematocrit, mean corpuscular volume and platelet values did not significantly differ between the patients survivors and non-survivors ($p = 0.058$, $p = 0.197$, $p = 0.951$, $p = 0.321$, $p = 0.058$ and $p = 0.873$, respectively). However, the median age, CRP, CAR, neutrophil, NLR, monocyte / lymphocyte ratio (MLR), RDW-CV and RDW-SD were significantly higher ($p <0.001$, $p = 0.034$, $p = 0.015$, $p <0.001$, $p <0.001$, $p <0.001$, $p = 0.025$ and $p = 0.002$, respectively); and the median albumin, lymphocyte and eosinophil values were significantly lower in patients non-survivors ($p = 0.004$, $p <0.001$ and $p <0.001$, respectively), compared with the patients survivors.

Table 1. Mortality rates of acute ischemic stroke according to affected blood vessels

Vascular location of cerebral infarction	Survivors n (%)	Non-survivors n (%)	Total (100%) n
Multiple cerebral arteries	28 (90.3%)	3 (9.7%)	31
MCA - M1	15 (27.5%)	25 (62.5%)	40
MCA - M2 anterior branch	30 (75%)	10 (25%)	40
MCA - M2 posterior branch	50 (79.4%)	13 (20.6%)	63
ACA - A1	2 (66.7%)	1 (33.3%)	3
ACA - A2	2 (66.7%)	1 (33.3%)	3
PCA - P1	20 (90.9%)	2 (9.1%)	22
PCA - P2	19 (95%)	1 (5%)	20
Total basilar artery infarction	6 (60%)	4 (40%)	10
Pons perforators of basilar artery	43 (87.8%)	6 (12.2%)	49
LSA	34 (94.4%)	2 (5.6%)	36
Superior cerebellar artery	16 (84.2%)	3 (15.8%)	19
Massive ICA region infarct	2 (25%)	6 (75%)	8
Total	267 (77.6%)	77 (22.4%)	344

MCA, Middle Cerebral Artery; LSA, Lenticulostriate Arteries; ICA, Internal Carotid Artery; ACA, Anterior Cerebral Artery; PCA, Posterior Cerebral Artery

Table 2. Comparison of laboratory (blood) parameters between survivors and non-survivors

	Survivors	Non-survivors	P-value
Age (years)	72 (24 - 98)	79 (47 - 99)	<0.001
RBC (10^{12}/L)	4.87 ± 0.67	4.7 ± 0.66	0.046
CRP (mg/L)	4.52 (0.12 - 207.16)	6.79 (0.5 - 155)	0.034
Albumin (g/dL)	4.01 (2.6 - 5)	3.88 (2.12 - 4.79)	0.004
CAR	1.07 (0.03 - 57.82)	1.76 (0.14 - 46.95)	0.015
WBC (10^9/L)	9.03 (3.98 - 19.60)	9.43 (4.72 - 23.90)	0.058
Neutrophil (10^9/L)	5.84 (1.30 - 17.12)	7 (2.30 - 22.78)	<0.001
Lymphocyte (10^9/L)	2.12 (0.49 - 7.04)	1.58 (0.4 - 4.59)	<0.001
NLR	2.70 (0.40 - 21.40)	4.85 (0.8 - 23.88)	<0.001
Monocyte (10^9/L)	0.59 (0.09 - 2.56)	0.58 (0.11 - 2.04)	0.951
MLR	0.29 (0.04 - 1.27)	0.35 (0.10 - 3.22)	<0.001
Eosinophil (10^9/L)	0.11 (0.001 - 2.36)	0.05 (0.001 - 0.49)	<0.001
Hemoglobin (g/dL)	13.8 (6.8 - 18.7)	13.7 (9.3 - 16.8)	0.197
Hematocrit (%)	40.9 (24.4 - 57.2)	41.6 (28.3 - 51.2)	0.321
RDW-CV (%)	13.3 (9.6 - 26.1)	14 (10.2 - 23.4)	0.025
RDW-SD (fL)	42.9 (26 - 70)	45.3 (26 - 71)	0.002
MCV (fL)	87 (53.2 - 98.9)	89.5 (66 - 102.8)	0.058
Platelet (10^9/L)	228 (89 - 510)	229 (101 - 426)	0.873

CRP, C- Reactive Protein; RBC, Red Blood Cell; CAR, C-Reactive Protein / Albumin Ratio; NLR, Neutrophil / Lymphocyte Ratio; MLR, Monocyte / Lymphocyte Ratio; RDW, Red Blood Cell Distribution Width; MCV, Mean Corpuscular Volume; WBC, White Blood Cell

The Chi-square test showed that the gender distribution was not different between the patients non-survivors and survivors (p= 0.146). Additionally, the rates of congestive heart failure, hypertension, diabetes mellitus, hyperlipidemia and coronary artery disease did not significantly differ between the patients non-survivors and survivors (p = 0.485, p = 0.101, p = 0.458, p = 0.34 and p = 0.243, respectively) (Table 3).

Table 3. Comparison of risk factors between survivors and non-survivors

	Survivors (n = 267)	Non-survivors (n = 77)	P-value	X^2-value
Gender (M/F)	122/145	28/49	0.146	2.11
DM, n (%)	99 (37.1%)	25 (32.5%)	0.458	0.551
HT, n (%)	223 (83.5%)	58 (75.3%)	0.101	2.684
HL, n (%)	66 (24.7%)	15 (19.5%)	0.34	0.911
CHF, n (%)	28 (10.5%)	6 (7.8%)	0.485	0.487
CAD, n (%)	46 (17.2%)	9 (11.7%)	0.243	1.366

CAD, Coronary Artery Disease; DM, Diabetes Mellitus; CHF, Congestive Heart Failure; HL, Hyperlipidemia; HT, Hypertension

Table 4 shows the detailed results of univariate and multivariate logistic regression analyzes. In the univariate logistic regression model, the age, albumin, CAR, WBC, neutrophil, MLR, lymphocyte, NLR, eosinophil and RDW-SD were prognostic factors of mortality (p <0.001, p <0.001, p = 0.035, p = 0.005, p <0.001, p<0.001, p <0.001, p <0.001, p = 0.014 and p = 0.002, respectively). However, only RDW-SD and albumin were found to be prognostic factors of mortality in the multivariate logistic regression model (p = 0.005 and p = 0.021, respectively).

Table 4. Results of logistic regression analysis performed to determine prognostic factors

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.047 (1.022-1.074)	<0.001	1.021 (0.993-1.05)	0.145
Albumin	0.368 (0.224-0.605)	<0.001	0.427 (0.207-0.879)	0.021
CAR	1.034 (1.002-1.068)	0.035	1.154 (0.888-1.499)	0.284
WBC	1.111 (1.032-1.195)	0.005	0.846 (0.572-1.253)	0.404
Neutrophil	1.191 (1.103-1.286)	<0.001	1.301 (0.867-1.954)	0.204
Lymphocyte	0.475 (0.34-0.665)	<0.001	1.084 (0.575-2.041)	0.804
NLR	1.218 (1.136-1.307)	<0.001	1.092 (0.937-1.273)	0.261
MLR	10.89 (3.78-31.34)	<0.001	3.164 (0.594-16.862)	0.177
Eosinophil	0.051 (0.005-0.55)	0.014	0.684 (0.144-3.263)	0.634
RDW- SD	1.061 (1.021-1.102)	0.002	1.068 (1.02-1.118)	0.005

Mean corpuscular volume	1.035 (0.996-1.076)	0.076	1.012 (0.97-1.056)	0.583
C- reactive protein	1.008 (0.999-1.017)	0.088	0.951 (0.881-1.028)	0.207
Hypertension	1.66 (0.901-3.058)	0.104	-	-
Coronary artery disease	1.573 (0.732-3.377)	0.246	-	-
Hemoglobin	0.914 (0.803-1.040)	0.171	-	-
RDW-CV	1.091 (0.977-1.218)	0.12	-	-

Cox&Snell pseudo-R2 = 0.191, Nagelkerke pseudo-R2 = 0.292, Hosmer- Lemeshow P = 0.867. Level of significance is defined as P < 0.05. CAR, C-Reactive Protein / Albumin Ratio; WBC, White Blood Cell; NLR, Neutrophil / Lymphocyte Ratio; OR, Odds Ratio; RDW, Red Blood Cell Distribution Width; MLR, Monocyte / Lymphocyte ratio

Figure 1 shows the ROC curve representing the predictive value of RDW-SD and albumin for mortality. The areas under curve were: RDW-SD (increased) 0.613 (95%CI, 0.53-0.69) and albumin (decreased) 0.607 (95% CI, 0.53-0.68). The cut- off value of RDW-SD was found as 43.35 (sensitivity: 64% and specificity: 52%), and the cut- off value of albumin was found as 3.95 (sensitivity: 62% and specificity: 55%).

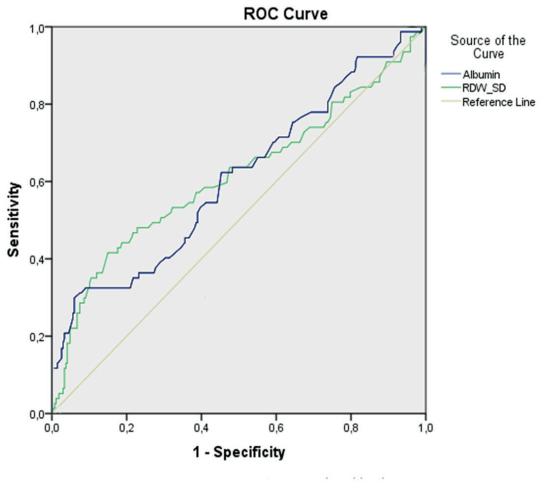

Figure 1. ROC curve representing the predictive value of RDW-SD and albumin for mortality

DISCUSSION

In this study, multivariate analysis showed that a high RDW-SD and a low albumin level at admission were associated with a poor prognosis in patients with acute IS. Moreover, NLR and CAR were found to be associated with a poor prognosis according to the univariate analysis, whereas no such association was observed in the multivariate analysis. Artery occlusions with the highest mortality rates were as follows: massive infarcts in the ICA area, MCA-M1 segment infarctions and total basilar artery infarcts (75%, 62.5% and 40%, respectively).

RDW is a blood parameter that shows anisocytosis, in other words, the change in erythrocyte diameter (17). There are 2 methods to evaluate RDW: using the standard deviation of red blood cell distribution width (RDW-SD, fL) and coefficient of variation for red blood cell distribution width (RDW-CV, %) (18). It has been underlined that RDW, which has been shown to be associated with inflammatory markers such as erythrocyte sedimentation rate and CRP, is a parameter indicating inflammation (4, 19). Several recent studies have reported that high RDW was associated with the stroke development (20) and was a poor prognostic factor in patients with acute IS (3, 20, 21). Unlike these studies, it was found in another study that RDW did not predict the severity and functional outcome of stroke in the early phase of acute IS (22). In this study, multivariate regression model showed that high RDW-SD at the time of admission was an independent poor prognostic factor for in-hospital mortality in patients with IS. In the light of the data obtained in this study, it was thought that RDW-SD at the time of admission could be used as a prognostic marker in patients with acute IS.

Albumin is known to be an acute phase protein that reflects systemic inflammation. Decreased serum albumin levels can be observed in systemic inflammation (12, 13). Previous studies have shown that a low serum albumin level was associated with a poor prognosis in IS (23, 24). In another study, it has been reported that high serum albumin levels led to a decreased risk of poor outcome in patients with IS (25). Similar to the previous studies, this study also showed that low albumin level at admission was an independent poor prognostic factor for in-hospital mortality in patients with acute IS.

Although previous studies reported that a high NLR (3, 5, 6) and CAR (10) were poor prognostic factors for IS, multivariate regression analysis of this study showed that they were not independent prognostic factors. This was thought to stem from the fact that the subjects included in this study were only the patients who had cerebral vascular occlusion that caused mortality or that the study was conducted with laboratory data which was obtained in the very early phase of IS.

Severity of stroke (2) and infarct volume (26) are the most important factors that affect the prognosis of IS. Infarcts due to basilar artery occlusion constitute 1-4% of all IS cases (27). However, such infarcts have a high mortality rate. In a previous study, it has been found that 29.6% of basilar artery infarcts resulted in death (28). In this study, 40% of all acute ISs secondary to basilar artery occlusion resulted in death. It is known that malignant MCA infarcts also have a very high mortality rate (3-month mortality nearly 45%) (29). This study also showed that malignant infarcts in the ICA area and malignant MCA-M1 infarcts had very high mortality rates (75% and 62.5%, respectively). In the light of the data obtained in this study, patients with acute IS who have such major cerebral vascular occlusions that are associated with high mortality should be promptly transferred to stroke centers for mechanical thrombectomy.

The significance of this study was that it only included the patients who had cerebral artery occlusion that caused mortality. Patients with minor artery occlusion that did not cause mortality (such as the patients with minor stroke) were not included in the study. Therefore, this study was conducted with a more homogenous population than the previous studies. Limitations of this study were as follows: the number of subjects included in the study to determine vascular mortality rates was low and the study was retrospective.

CONCLUSION

This study highlighted that high RDW and low albumin levels at admission are independent poor prognostic factors for in-hospital mortality in patients with acute IS. In addition, more multicenter studies with larger patient populations are needed to determine vascular mortality rates in IS.

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